

IN-DEPTH REVIEW

Future advances in work-related asthma and the impact on occupational health

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Abstract Work-related asthma (WRA) and WRA-like conditions refer to all situations in which asthma or asthma-like syndromes occur or worsen in the workplace. This occurs in ~10% of all adult-onset asthma subjects. Occupational asthma (OA) is a specific type of WRA that is ‘caused’ by the workplace, being mediated either by an allergic process with a latency period or by a non-allergic irritant-induced mechanism. Personal asthma can also ‘worsen’ at work (work-aggravated or exacerbated asthma), the reasons, mechanisms, extent and consequences of this situation being unknown. The author reviews various aspects of WRA with an emphasis on OA (about which more is known) and proposes key issues that need to be further studied, proposed and applied in at-risk workplaces in order to improve recognition, diagnosis and management of this condition. OA represents a unique situation that, unfortunately, is only very rarely provided to health-care providers: affected workers can be cured with minimal impact on quality of life. All efforts should be made to achieve this goal at an affordable socio-economic cost.

Key words Airway responsiveness; occupational asthma.

Introduction

Asthma, along with diseases due to asbestos exposure, is the most common occupational respiratory disease [1,2]. Nearly 10% of all adult-onset asthmatic subjects report that their asthma is worse at work [3]. Because asthma is a common chronic disease, it is relevant to rule out the possibility that it is caused by occupation, in the same way household environmental causes are examined. Although there are various means to ascertain the diagnosis, they are used either insufficiently [4] or incorrectly. While surveillance programmes are commonly mandatory in workers exposed to inorganic dusts causing pneumoconiosis, they are seldom proposed for work-related asthma (WRA).

This article will focus on some key issues that might well be developed in future years and have an impact on occupational health. The items that will be presented are summarized in Table 1.

Definition and classification

WRA refers to at least two nosological entities [5] (Figure 1). The first is occupational asthma (OA) as such, defined as a type of asthma ‘caused’ by the workplace. The causal mechanism can be either allergic, for asthma

that occurs after a latency period needed to acquire allergic sensitization, or irritant induced, as in the case of accidental inhalational exposure to products with irritant properties encountered in the workplace. The second entity is personal asthma that apparently ‘worsens’ at work due to other causes (work-aggravated or exacerbated asthma). So little is known about the latter condition that it is the author’s impression that almost everything needs to be done in terms of diagnosis, epidemiology, socio-economic issues, etc. Finally, although not included in WRA as such, there are several variants of asthma that are related to working conditions, such as potroom asthma and grain dust fever. These apparently share at least one or more ‘asthmatic’ features but cannot be considered WRA conditions.

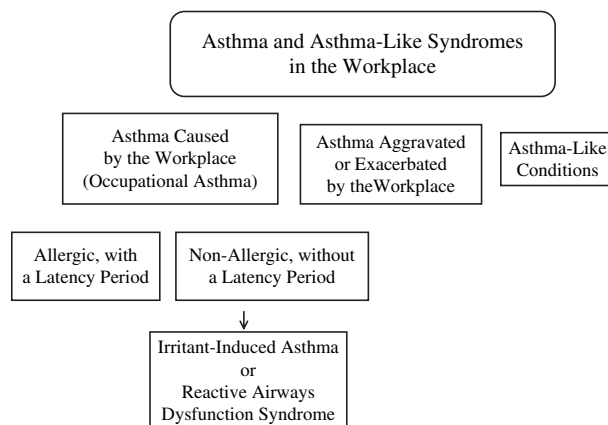
More attention has been directed to the allergic type of OA than to other forms of WRA, thanks to the pioneering work of Pepys and Bernstein [6]. In recent years, some, but still too little, attention has been focused on the other type of OA, that is non-allergic irritant-induced asthma [7–9]. In particular, we do not know whether multiple irritant exposures at lower concentrations can result in the same damage as a single high-level exposure. Objective evidence of worsening of asthma at work (work-aggravated or exacerbated asthma) is generally anecdotal. Workers report that their asthma is worse at work and they use bronchodilators on demand. However, as a rule, there is no documented objective evidence of this worsening. Nor do we know whether this temporary effect results in long-term deterioration of asthma with more

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Table 1. Key issues and possible developments in work-related asthma (WRA)

Domain	Key issues	Possible developments
Definition	Where does work-aggravated or exacerbated asthma stand in relation to asthma caused by the workplace (OA)?	Research more focused on irritant-induced OA Examine all aspects of asthma aggravated or exacerbated by the workplace
Physiopathology	What are the genetic determinants? Do neutrophils play a role? How do low-molecular-weight agents cause OA? Can this be predicted? What is the mechanism of irritant-induced OA?	WRA becomes an ideal model for examining the epigenetics (environment–gene interaction) of asthma Chemicals are targeted as possibly asthmagenic before entering the workplace Early treatment can make cure feasible in the case of irritant-induced asthma
Workplace environment	Lowering exposure is the first target Interaction of common pollutants, endotoxins and workplace ‘allergenic’ products	Standards for maximum concentrations set for key occupational allergenic products Lowering the levels of non-specific irritants will lower the frequency of sensitization to occupational agents
Epidemiology and surveillance	Longitudinal data give key information on worldwide trends in frequency and nature of occupational agents Should surveillance be proposed and, if so, when in relation with entering the workplace? Focus on early diagnosis and referral	Worldwide databases to be made available Simple and affordable means (biological, psychological) to identify and characterize cases early and surveillance programs tested in the first 2 years
Diagnosis	Insufficiently and incorrectly diagnosed condition in most countries; based too often on responses to questionnaires only	Objective means and new tests more widely used
Medicolegal and socioeconomic aspects	Protection and management of workers insufficient; mandatory advice to stop or at least reduce exposure	Assessments of socioeconomic impacts of OA worldwide to be carried out. Permanent disability scales to be re-visited. Efforts to be made to cure the disease

**Figure 1.** Asthma and asthma-like syndromes in the workplace.

airway obstruction, hyperresponsiveness and inflammation. If such an effect is demonstrated, it will change our approach to treating asthmatic subjects who experience worsening of asthma at work. More information on the pathophysiology and pathological airway changes that occur in variants of asthma at work (as discussed earlier) may change our approach to these conditions. To what extent should these conditions be classified in the ‘asthmatic’ category? What features do they really share with asthma?

Mechanisms

Recent tremendous and overwhelming developments in the genetics of disease have not yet contributed to significant breakthroughs in the specific cases of asthma and, consequently, OA. Much information remains fragmentary, unconfirmed and unreplicated [10]. As reviewed [11], only a few HLA polymorphisms have been suspected of being associated with certain types of OA caused by chemical agents, and in those cases, the findings have not necessarily been replicated.

As for asthma, the recent focus has been on the role of cytokines and other cells such as neutrophils [12–14], besides lymphocytes and eosinophils, which are recognized as key cells in asthma. Whereas endotoxins seem to exert a protective effect in the development of asthma [15], they seem to be associated with the presence of symptoms in animal handlers who are not sensitized to animal-derived allergens [16]. The asthmagenic mechanism of low-molecular-weight agents that currently represent at least half of the agents causing OA (see www.asthme.csst.qc.ca and www.asmanet.com) is still lacking for most agents [17]. The asthmagenic potential of these low-molecular-weight agents (chemicals) has just begun to be explored [18,19]. Whereas an IgE-mediated mechanism has clearly been demonstrated for high- and

some low-molecular-weight occupational agents, IgG levels, in particular IgG4, can also be increased, as a consequence of exposure, the disease or both [17]. Epithelial shedding and airway remodelling are features of irritant-induced asthma [9].

It would be of great interest to initiate studies in epigenetics, a science that examines stable alteration in gene expression, a potential that derives during development and cell proliferation. WRA can therefore become a suitable model to examine environmental–genetic interactions. Psychological factors that may favour the onset of the symptomatology of WRA should be documented, especially for asthma exacerbated by the workplace. If endotoxins exert a protective role in the development of asthma and, possibly, of WRA, it would be worthwhile to consider environmental approaches that, together with occupational allergen reduction, would diminish the risk of developing WRA. The asthmagenic properties of new chemicals entering workplaces, as well as of repeated exposures at work to products with irritant properties generated in peaks, warrant assessment. Examining biopsy samples of subjects with apparently cured OA might yield information on the possibility that inflammation still persists together with airway remodelling. The role of epithelial and fibrogenic factors in irritant-induced asthma should be examined [20,21].

Environmental exposure

Exposure is the most important determinant of WRA. However, the best method to characterize the environment in relation to WRA (relevance of mean and peak exposures) is still open to debate [22]. Monitoring should include not only inhalable material but also, possibly, material that can be absorbed through the skin, as there is a suggestion that this can occur [23,17]. As for isocyanates more specifically, all isocyanate functions should be considered in environmental monitoring since these agents can cause asthma whether they exist as monomers or polymers [24]. Many studies have convincingly demonstrated an interaction between pollutants and allergens in promoting sensitization and non-OA. This is probably the situation for occupational allergens as well, but we have no information on this issue.

Monitoring of the workplace environment has an important consequence in terms of prevention and of the establishment of prevention programmes (see subsequently). Although environmental standards have been proposed for some occupational agents such as wheat dust [22] and isocyanates, such standards should be proposed for all commonly encountered occupational agents that may cause WRA.

Epidemiology and health surveillance

Frequency of WRA has been examined in case series and at-risk populations through cross-sectional surveys that

generated prevalence figures. Incidence data obtained from sentinel projects [2,25], national data statistics [26] and prospective studies in the general population [27] and at-risk populations [28] are now more widely available. Such information is representative of trends in disease frequency and also gives important clues on the nature of agents that cause OA and that can vary with time. A meta-analysis has shown that ~10% of all adult-onset asthma can be attributed to the workplace [3]. Very few surveillance programmes have been carried out [29,30]. Although WRA is common (as discussed previously), there are those who wonder if health surveillance would really be useful and effective in WRA [30]. Although two programmes have proved to be effective—in workers exposed to enzymes in a large industry [31] and in health workers who are currently less exposed to latex due to the use of latex-free or -reduced and powder-free gloves [32]—the usefulness of a programme in workers exposed to isocyanates showing a reduction in the number of cases might be questioned on the grounds that such a reduction in cases of OA due to isocyanates has also been documented in other countries where no surveillance programme was applied [33]. As regards primary prevention, it is evident that atopy should not be a proposed marker because it is too common, with ~50% of young atopic adults entering at-risk occupations [34] and in the general population. The natural history of OA is different for high- and low-molecular-weight agents: with high-molecular-weight agents, most cases become sensitized in the first 2 years after starting exposure [35], whereas symptoms generally develop more slowly with low-molecular-weight agents [36]. Workers can develop symptoms at any time during their careers, which makes all surveillance programmes difficult to apply. The efficacy of such prevention programmes may be greatly hampered by psychological and cultural factors. Regarding secondary prevention, cases have to be identified early, as it is well known that in cases of OA with a latency period, the earlier the worker is removed from the workplace, the more likely she/he is to be cured [30]. This, of course, does not apply to irritant-induced OA, for which measures to reduce the likelihood of accidental inhalational episodes should be proposed.

Better field means should be developed by molecular biologists for the early identification of cases of sensitization to occupational agents. Surveillance programmes combining an environmental approach with a multidisciplinary health intervention should be proposed in high-risk workplaces in order to diminish the impact, though probably (and unfortunately) not the incidence of the disease. Research on behavioural aspects related to risk has to be encouraged in order to change self-perceptions on risk [37]. Prospective cohorts of apprentices or workers starting in high-risk fields need to be assembled to better examine the natural history of sensitization to oc-

cupational agents, OA and asthma. National databases should be set up to serially examine the trends in the disease worldwide.

Diagnosis

When expensive and sophisticated diagnostic methods are available for most health conditions, OA too often remains undiagnosed [27] and incorrectly or insufficiently investigated by clinical and functional means. Diagnosis of OA is based on a stepwise approach: questionnaire, immunological assessment (when relevant and feasible), lung function and inflammatory tests and specific inhalation challenges [38]. Contrary to common belief, such investigation is not unduly expensive when measured against the fruitfulness of the approach. Although the validity of some tests, such as peak-flow monitoring [39] and specific inhalation challenge [40], has been examined in several studies, questionnaires and inflammatory tests have not been thoroughly evaluated. Questionnaires are more helpful in the case of high- than low-molecular-weight agents, as the former agents often cause nasoconjunctival symptoms as well [41]. The diagnosis of OA should be confirmed by objective evidence because it has important health and socio-economic consequences, as when advising young individuals to change careers or to stay at work, with the possibility that their asthmatic condition might worsen and lead to permanent sequelae. OA is too often diagnosed only by examining answers to a questionnaire and information on possible 'sensitizers' in the workplace, which is unacceptable by comparison with fancy and expensive diagnostic means used for other health conditions. Improved methodology has been proposed for specific inhalation challenges, which, for many, represent the 'gold standard' of diagnostic tools, and the accuracy and safety of such tests have been assessed. Tests such as induced sputum examination, which reflects the status of inflammation, should no longer be reserved for research but now be proposed for clinical diagnosis [42]. Diagnosis of irritant-induced asthma will remain dependent on a clinical history and on the persistence of airway obstruction and/or hyper-responsiveness [9].

Diagnostic services for WRA should be more widely available and used, especially in remote centres. Objective tests can be performed at large centres, but the interpretation should be referred to highly specialized centres. Specific inhalation challenges should be carried out according to quality control standards in selected certified centres.

Medicolegal and socio-economic aspects

Although OA is a condition that is under the jurisdiction of medicolegal authorities in most countries [43], exam-

ination of cases is often unsatisfactory and takes time. The protection offered to workers is generally inadequate. Affected workers frequently continue to be exposed or, if not, encounter serious socio-economic losses [44–46]. Workers with OA are generally young and retraining is often mandatory.

Diagnosis should be made precisely and with minimal delays to provide accurate and efficient advice. Once the diagnosis is made, the worker should be assessed and a suitable readaptation programme offered. In young individuals, this might mean returning to school to complete undergraduate studies and entering professional programmes in which, ideally, they are no longer exposed to the causal agent. If such proposals are made, it has been estimated that the quality of life of workers with OA will be satisfactory [47], and at an acceptable socio-economic cost [43]. The advice to the workers should minimally be to reduce exposure if complete removal cannot be achieved, although it should be clearly stated that deaths have been reported in subjects who remain exposed [48]. Interestingly, persisting airway obstruction after removal from exposure to the causal agent does not seem to have a major impact on the capacity of workers with OA to find a new job, but education, age (young or old) and working in small companies do [49]. The outcome of workers whose asthma symptoms are aggravated at work is unsatisfactory, as many leave the workplace even after being told that they do not suffer from OA [46]. As mentioned earlier, considerable research has to be carried out to identify the factors that incite these workers to leave work and propose remedies. Inadequate control of 'personal' asthma may be one of these factors, and appropriate treatment of the asthmatic condition should be determined and applied.

The natural history of OA after removal from exposure shows that the majority of workers present symptoms and functional abnormalities even after they are completely removed from exposure. Even in apparently cured subjects, airway inflammation can still persist long after stopping exposure [14]. Early treatment with inhaled anti-inflammatory agents can hasten improvement [50]. In the case of OA with a latency period, the maximum improvement occurs in the first 2 years or so after stopping exposure, but there is still improvement, though at a slower pace, thereafter [51]. In the case of irritant-induced asthma, the pattern of improvement seems similar to OA with a latency period, at least in the first 2 years after the inhalational accident [52].

There should also be provisions to allocate permanent disability to workers left with permanent asthma, although this has a much lesser impact than accurate readaptation programmes judiciously applied in the first 2 years after cessation of exposure. A scale based on the need for medication, airway calibre and responsiveness has been proposed [53] and now adopted by official organizations [54,55]. The handicap of not being able

to carry on one's usual work should also be considered in the compensation scheme.

More cost-benefit data on the socio-economic impact of OA should be gathered worldwide. What are the functional consequences of reducing exposure if inhaled steroids at acceptable doses are prescribed? Optimal readaptation scheme programmes should be proposed to affected workers in order to minimize the impact of the condition. The validity of including other items besides airway calibre and responsiveness, as well as the need for asthma medication, in the permanent disability assessment should be explored. These include psychosocial impact assessed by specific questionnaires, as well as quality of life.

Conclusion

For a long time, asthma was considered a benign condition until society as a whole became aware of its sizeable impact in terms of frequency, morbidity and even mortality. WRA unfortunately still suffers from the same denial, probably because other work-related occupational lung diseases such as pneumoconiosis and cancers may have a greater health impact. However, OA is a condition that can be cured if the diagnosis is made rapidly. It can have minimal impact on one's health and life if adequate readaptation is proposed. Finally, OA usually affects young people, so efforts to cure it have a long-term effect. To date, OA with a latency period has warranted the most attention. Other conditions, such as irritant-induced asthma and asthma aggravated or exacerbated at work, should now drive our research and management efforts.

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Conflicts of interest

None declared.

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